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| 09/581,241      | 06/26/2000  | NORIAKI HATTORI      | 193582US0PCT        | 3276             |

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EXAMINER

SLOBODYANSKY, ELIZABETH

ART UNIT PAPER NUMBER

1652

DATE MAILED: 09/10/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/581,241

Applicant(s)

HATTORI ET AL.

Examiner

Elizabeth Slobodyansky

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 14 June 2002.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 14-33 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-20, 22, 24, 25 and 27-33 is/are rejected.
- 7) ☒ Claim(s) 21, 23, 26 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413) Paper No(s). \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_

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### **DETAILED ACTION**

The amendment filed June 14, 2002 amending the specification to remove brackets in the subtitles, canceling claims 1-13 and adding claims 14-33 has been entered.

Claims 14-33 are pending.

### ***Priority***

Receipt is acknowledged of an English translation of JP 361022/97 submitted under 35 U.S.C. 119(a)-(d). However, a statement that the translation of the certified copy is accurate in accordance with 37 CFR 1.55 is lacking. See MPEP § 201.15.

### ***Claim Objections***

Claim 14 is objected to because of the following informalities: the name "Coleoptera" is different from "Cleoptera" given on page 6, line 2. Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly

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connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-20, 22, 24, 25 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 14 is directed to a mutant luciferase of any structure and properties having improved luciferase activity in the presence of a surfactant compared to a luciferase in which a mutation has not been introduced, wherein said non-mutated luciferase derived from an organism belonging to Order Coleoptera. Order Coleoptera includes several Families of organisms having different physiological and biochemical properties. Dependent claim 15 limits the organism's origin to Family Firefly. While referring to the luciferase from *Luciola lateralis* (HEIKE) or *Luciola cruciata* (GENJI), claim 20 does not impart any limitation on the structure except for the mutation at position 490. Claims 22 and 24 recite a polypeptide comprising additions, deletions, or substitutions in SEQ ID NOs:4 or 6. Since number of possible mutations is not limited, this amounts to any structure that is not necessarily homologous to SEQ ID NOs:4 or 6. Claims 16-19 limit surfactant and degree of luciferase activity. Claims 25-29 are drawn to a gene encoding a mutant luciferase of claim 14, a vector and a cell transformed with the same and a

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method for recombinant production of a mutant luciferase. Claims 30-33 are drawn to a method of use of a mutant luciferase of claim 14.

Thus, the claims are drawn to or depend from an enormous genus of a mutant luciferase having an improved activity in the presence of a surfactant. Said genus of mutants is characterized by function.

Applicants disclose two mutants of *L. lateralis* luciferase having an improved activity in the presence of a surfactant having sequences of SEQ ID NOs: 4 and 6 that comprise mutation E490K. (These two sequences differ by the mutation at 217 wherein SEQ ID NO:4 has A217L and SEQ ID NO:6 has A217I). Therefore, a representative number of a luciferase mutated at position 490 is two. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the "functionality" of having an improved activity in the presence of a surfactant and fails to provide any structure: function correlation present in all members of the claimed genus. Therefore, the specification is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

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Claims 14-20, 22, 24, 25 and 27-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for mutant *Luciola lateralis* luciferases having the sequences of SEQ ID NO:4 or SEQ ID NO:6 that are mutated at position 490 and have an improved activity in the presence of a surfactant and for mutant *Luciola cruciata* luciferases with corresponding sequences, does not reasonably provide enablement for a mutant luciferase having unknown homology to SEQ ID NO:4 or SEQ ID NO:6 and having an improved activity in the presence of a surfactant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, how to make the invention commensurate in scope with these claims.

Claim 14 is directed to a mutant luciferase of any structure and properties (the number of possible mutations is not limited) having improved luciferase activity in the presence of a surfactant compared to a luciferase in which a mutation has not been introduced. Dependent claims 16 and 17 recite specific surfactants while dependent claims 18-19 recite specific activity (89.3%) of said mutant luciferase.

Claims 14-20, 22, 24, 25 and 27-33 are so broad as to encompass any mutant luciferase with unknown possible low homology to the luciferase of *Luciola lateralis* having the requisite properties or any mutant luciferase with unknown possible low homology to the luciferase of *Luciola lateralis* having the requisite properties in which the amino acid corresponding to residue 490 is substituted, polynucleotides encoding

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for such mutant luciferases and methods of use of such mutant luciferases. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of mutant luciferase enzymes and genes broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and amino acid sequence of two mutant luciferases having one or two amino acids different compared with the wild-type sequence.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

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The specification does not support the broad scope of the claims which encompass any mutant luciferase having the requisite property with an undisclosed homology to the luciferase of *Luciola lateralis* and any mutant luciferase with no or low homology to the luciferase of *Luciola lateralis* in which the amino acid corresponding to residue 490 of *Luciola lateralis* luciferase is mutated or polynucleotides encoding therefor because the specification does not establish: (A) regions of the protein structure which may be modified without effecting luciferase activity; (B) the general tolerance of luciferases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any luciferase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

In addition, with regard to claims 18 and 19, the specification provides no direction as to how to make a mutant luciferase having a structure other than SEQ ID NO:4 or 6 having 89.3% activity when a surfactant other than benzalkonium chloride is used (page 19, Table 1).

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of amino acid modifications of any luciferase with no or low homology to the luciferase of *Luciola lateralis* having



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the desired properties in which the amino acid corresponding to residue 490 is or is not mutated. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of luciferases and genes therefor having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 14, with dependent claims 15-20, 22, 24-33, is rejected under 35

U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is confusing because it is drawn to an isolated "mutagenized" polypeptide, said isolated polypeptide is derived from an organism belonging to Order Coleoptera. There is a contradiction between the claimed polypeptide being a mutant and at the same time being derived from an organism. Amending the claim to refer to a mutant polypeptide wherein a wild-type polypeptide derived from an organism, for example, is suggested. Further, claim 14 recites "compared to a luciferase in which a mutation has not been introduced". It is unclear what is encompassed by said non-

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mutated luciferase in addition to the wild-type luciferase rendering the metes and bounds of the claim unclear.

Claim 20 is indefinite for their recitation of the 490 amino acid position without indicating a sequence identifier of the sequence where said position is located. Reference to SEQ ID NO: of a wild-type luciferase would obviate this rejection.

### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

Claims 14-20, 22, 24, 25 and 27-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Hirokawa et al.

The applied reference has a common assignee and one common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of

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this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Hirokawa et al. (US Patent 6,074,859) teach mutant luciferases having improved activity compared with the wild type luciferase. The activity is measured in buffers containing surfactants such as HEPES, CHES, Mes, TAPS, ammonium sulfate, etc (for example, columns 12-13). Furthermore, Hirokawa et al. teach SEQ ID NO: 14 that has 99.8% identity to SEQ ID NO:4 and 99.7% identity to SEQ ID NO: 6 of the instant invention. SEQ ID NO:4 of the instant invention differs from SEQ ID NO:14 disclosed in the Hirokawa et al. patent only by substitution T219I. SEQ ID NO:6 of the instant invention differs from said sequence by two substitutions L217I and T219I. Both Hirokawa et al. sequences have E490K substitution. Said mutant luciferase has an improved activity compared with the wild-type luciferase in buffers containing surfactants. Hirokawa et al. teach methods for measuring ATP using luciferase (Example 5).

### ***Response to Arguments***

Applicant's arguments filed June 14, 2002 have been fully considered but they are not persuasive.

Applicants argue that "Hirokawa et al is not entitled to priority under 35 U.S.C. § 119 (e) to Provisional Application Number 60/051,917" (page 8). Since the Sequence

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Listing in 60/051,917 is not submitted in the CRF, the examiner is unable to align the sequences therein with the sequences in the instant application. However, 60/051,917 discloses mutant luciferases having an improved activity in HEPES buffer, for example (page 4, last paragraph, for example). "Surfactant" is defined in the specification by non-limiting example that does not exclude HEPES (page 11). Thus, while 60/051,917 may not have support for SEQ ID NO:4 or 6, it provides support for a mutant luciferase of any structure with the requisite property. Furthermore, the English translation of the priority document needs certification, *supra*.

With regard to the written description, Applicants argue that "the claimed luciferase is clearly specified by defining an origin and by reciting "recombinant and mutagenized". Further, the invention specifies the surfactant and defines "resistance to a surfactant"" (page 10, lines 1-3). This is not persuasive because the origin becomes irrelevant since the number of mutations is not limited. Therefore, the mutant is not described by structure with exception of SEQ ID NOs: 4 and 6 or by correlation between function and some structural elements.

Applicants further argue that "the degree of the improvement in luciferase resistance was unpredictable" (page 10, lines 7-8). The examiner agrees with that. That is what renders the entire scope of invention not enabled. The mutants having the sequences of SEQ ID NOs: 4 and 6 were empirically found. Applicants argue that they "have disclosed a particular screening process to obtain the claimed luciferase" (page

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11, last line). This is not persuasive, because while the screening process is enabled, the making a mutant luciferase of any structure with the requisite property is not.

### ***Allowable Subject Matter***

Claims 21, 23 and 26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form.

### ***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

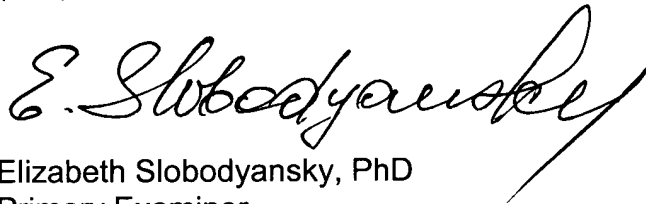
A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth Slobodyansky whose telephone number is (703) 306-3222. The examiner can normally be reached Monday through Friday from 9:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy, can be reached at (703) 308-3804. The FAX phone number for Technology Center 1600 is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Center receptionist whose telephone number is (703) 308-0196.

A handwritten signature in black ink, appearing to read "E. Slobodyansky", with a long, sweeping horizontal stroke extending to the right.

Elizabeth Slobodyansky, PhD  
Primary Examiner

August 30, 2002